Remarks

Response to objection to specification and rejection of claims 5, 6, 13, 14, and 41 under 35 U.S.C. § 112, first paragraph for insufficient written and guidance.

The Examiner, at page 2 of the Office Action, has objected to the specification and rejected claims 5, 6, 13, 14, and 41 under 35 U.S.C. § 112, first paragraph, asserting that the application fails to provide sufficient written description and guidance for how one uses the conjugates as claimed. The Examiner further indicates that the rejection stands on reasons of record. Applicants traverse the objection and rejection for the following reasons.

Applicants respectfully point out that, contrary to the assertion of the Examiner, these claims are composition claims, not method claims, therefore the rejection of the Examiner is not appropriate. However, in order to expedite prosecution of the application, Applicants will demonstrate that composition claims 5, 6, 13, 14, and 41 are supported by more than ample written description. Claims 5, 6, 13, 14, and 41 recite antibodies, or compositions comprising antibodies, wherein said antibodies are coupled to effector molecules selected from the group consisting of toxins, virucides and microbicides. Claims 6 and 14 further recite that the toxin is adenylate cyclase toxin.

In *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably

> conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). *Accord Regents of University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), cited by the Examiner. Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

In determining the sufficiency of support in a disclosure with respect to the written description requirement, "it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re Edwards*, 196 USPQ 465, 467 (C.C.P.A. 1978) (citing *In re Lukach*, 169 USPQ 795 (C.C.P.A. 1971); *In re Driscoll*, 195 USPQ 434 (C.C.P.A. 1977)). More recently, the Court of Appeals for the Federal Circuit, in *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983), citing *In re Edwards*, emphasized:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.

More recently, in *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit pointed out that literal support is not required in order to satisfy the written description requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. For example, in *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 227 USPQ 177, 180 (Fed. Cir. 1985), the trial court admitted expert testimony about known industry standards regarding temperature and pressure in "the art of both farinaceous and proteinaceous vegetable materials." The

> effect of the testimony was to expand the breadth of the actual written description since it was apparent that the inventor possessed such knowledge of industry standards of temperature and pressure at the time the original application was filed.

Therefore, it is clear that the invention need not be described in *ipsis verbis*, *i.e.*, literally, for purposes of the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is needed is that the skilled artisan understand, based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor had possession of the claimed subject matter.

Applicants respectfully submit that the skilled artisan would have understood, based upon the disclosure provided in the specification as filed, that the inventors had possession of the present invention as claimed. Furthermore, Applicants submit that claims reciting antibodies, or compositions comprising antibodies, wherein said antibodies are coupled to effector molecules selected from the group consisting of toxins, virucides and microbicides, further wherein the toxin is adenylate cyclase toxin, are supported by the specification as filed and satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, under current law.

Particularly, the claimed antibodies, or compositions comprising antibodies, are described by biological, chemical, and functional properties in the specification as filed, and general properties of antibodies are known in the art. In addition, the conditions to which the conjugates are targeted, as well as systems and modes of delivery, dosages, etc., are provided in the specification or such information was available to those of skill in the art at the time the specification was filed.

For example, Figure 1 provides a description of the preparation and cloning of an anti-sperm antibody used in the present invention (RASA) and its cloning into an expression vector (see also page 8, lines 21-25). The preparation of other types of antibodies, such as miniantibodies and antibody fragments is also provided throughout the specification (page 8, line 24 to page 11, line 24). Methods of modifying the antibody (page 11, lines 13-24), using the antibody as a spermistatic agent (page 11, line 25 to page 12, line 2), methods of delivery and formulation (page 12, line 3 to page 13, line 19; page 14, lines 1 to 6), dosages (page 13, lines 20 to 32), treating conditions such

as enhancing immunity for inhibiting fertilization or preventing or inhibiting the effects of exposure to measles, chicken pox, hepatitis, smallpox and tetanus (page 14, line 1 to page 15, line 2), diagnosis and therapy of diseases, disorders and conditions, including infertility and detection of the presence of sperm for applications such as forensics, and purification of sperm for forensic applications or for use in *in vitro* fertilization applications (page 15, line 3 to page 17, line 12; page 25, lines 1 to 24). Because an antibody of the invention binds to the sperm protein, SAGA-1, it is understood that when such an antibody is administered, it will target to sperm. When an agent is coupled to the antibody, it necessarily will be targeted to the same location. Thus, one of ordinary skill in the art would have known that at the time the application was filed that many agents could be coupled to antibodies. For example, at page 11, lines 17 to 24 of the specification it is stated:

> In one embodiment the antibody is linked to a bioactive agent that is capable of exerting a biological effect in vitro and/or in vivo. Bioactive agents include, for example, toxins, virucides and microbicides, therapeutic agents, pharmaceutical agents, drugs, synthetic organic molecules, proteins, peptides, oligosaccharides, steroids, steroid analogs, chelators or metal binding peptides, enzymes, peptides bearing a detectable label (e.g. a radioisotope or fluorophore) and genetic material, including nucleic acids. In one embodiment the recombinant antibody is coupled to an adenylate cyclase toxin or other toxin, like ricin.

Furthermore, methods of formulating pharmaceutical compositions, determining dosages, and delivery systems are known in the art and are described in publications such as Genaro, ed., 1985, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA. The properties described in the specification as filed and in the art more than satisfy the written description requirement and provide general biological activity characteristics to support any modifications or structures which are important for biological activity under 35 U.S.C. §112, first paragraph.

Additionally, many basic properties of the S19 antibody, from which the antibodies of the invention were derived, were already described in Herr et al., U.S. Patent No. 5,830,472 (cited by the Examiner).

Further evidence that use of antibodies coupled with other agents was known to those of skill in the art is found in Owens et al., J. Immunol. Methods, 1994, 168:149-

165, cited by the Examiner. At page 149, first column, Owens cites several articles regarding the use of conjugated antibodies as agents in the diagnosis and treatment of human diseases. Owens states that clinical applications have included the imaging of tumors with radiolabelled antibodies, passive immunotherapy in the treatment of viral infections, and immunosuppression. Bird et al., Science, 1988, 242:423-426, cited by the Examiner, also discusses the use of antibodies as an imaging or delivery agent (page 423, column 3).

Russell et al., U.S. Patent No. 6,080,560, cited by the Examiner, states at column 1, lines 12-23 that:

> The medical sciences are increasingly turning to purified mammalian antibodies as powerful diagnostic and therapeutic reagents. The ability to exploit the exquisite specificity of particular antibodies for their antigenic determinants has revolutionized the ways in which diseases are described, diagnosed and treated. For example, cancerous cells can be revealed by tagged antibodies directed against the cell-bound products of activated oncogenes. Cultured antibodies directed against unique epitopes on tumor surface antigens have been chemically coupled to cytotoxic agents and administered therapeutically.

Thus, references cited by the Examiner recognize that antibodies can be coupled with various kinds of agents, utilized in various research and clinical capacities.

Applicants also refer to the Declaration of Dr. Thomas Moench, submitted herewith, where at page 3, item 6, Dr. Moench states:

> I believe that one of skill in the art would "know for what condition a conjugate of a sperm-specific antibody with toxins, microbicides, or virucides would predictably function, other than delivery of a spermicidal toxin, in the absence of further description and guidance from applicant". Dependent claims 6 and 14 also specifically recite that the toxin is adenylate cyclase toxin. I believe that ample written description and guidance are provided in the specification as filed ant that one of ordinary skill in the art would understand what conditions are being targeted when toxins, microbicides, or virucides are conjugated to a sperm-specific antibody. It is known in the art that antibodies, as well as a wide variety other agents with varied modes of action, can be delivered for many uses, including contraception, disease treatment and disease prevention.

Dr. Moench goes on to recite some of his publications in this scientific area. For example, they showed that antibodies, as well at Fab and F(ab')2 fragments, can be

applied topically as protection against HSV-2 infection (Zeitlin et al., 1996, Virology, 225:213-215); that antibodies can provide protection against genital herpes (Zeitlin et al., 1998, Nature Biotechnology, 16:1-5); and that BufferGel can be used for contraception and prevention of sexually transmitted diseases (Zeitlin et al., 2001, Sex. Tansm. Dis. 28:417-423). Dr. Moench and co-workers also showed that membrane-modifying agents can be administered to block vaginal transmission of cell-associated HIV-1 (Khann et al., 2002, J. Clin. Invest., 109:205-211) and that bacterial vaginosis can be treated with a buffering vaginal microbicide (Mayer et al., Clin Infect Dis 2001, 32:476-82; van de Wijgert et al., J AIDS 2001, ;26:21-27). In fact, Dr. Moench's work specifically refers to viral and bacterial infections, contraception, virucides, microbicides, and toxins, and the use of antibodies. Thus, it is evident from Dr. Moench's work and his opinion as stated in his Declaration, as well as that of others, that various types of agents, including antibodies and antibodies conjugated with various agents, are useful for contraception, disease prevention, and disease treatment, and are known to those of ordinary skill in the art.

Applicants respectfully submit that each and every conjugate, method of delivery, dosage, and condition or disease to be diagnosed or treated need not be disclosed in order to satisfy the written description requirement. Indeed, in *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), the court held that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art."

Further, the adequacy of the disclosure provided in the specification must be considered in light of the advanced state of knowledge in the relevant art and because there has been extensive reduction to practice, *e.g.*, preparation and use of antibodies have been disclosed in the specification as filed, as have numerous biological properties of antibodies and antibody-agent conjugates been disclosed in the art.

Therefore, the disclosure in the instant application clearly apprises one skilled in the art that Applicants were in possession of the claimed invention at the time the specification was filed for purposes of 35 U.S.C. §112, first paragraph. This is because the skilled artisan, to whom the application is addressed, armed with the teachings provided by the specification as filed and the knowledge of the prior art, would have reasonably understood that the invention encompasses antibodies, or compositions

comprising antibodies, wherein said antibodies are coupled to effector molecules selected from the group consisting of toxins, virucides and microbicides, further wherein the toxin is adenylate cyclase toxin. This is especially true where the specification provides extensive reduction to practice, including, but not limited to, working examples of the claimed antibodies and compositions, and numerous assays that can be used to prepare additional antibodies and antibodies coupled with effector agents. Given the advanced state of the relevant art and the extensive disclosure provided by the specification as filed, claims 5, 6, 13, 14, and 41 are amply supported and satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Based on the specification as filed, as well as what was known in the art at the time the application was filed, one of ordinary skill in the art would have understood how and when a recombinant antibody, coupled to an effector molecule such as a toxin, a virucide, or a microbicide, or a composition thereof, as recited in claims 5, 6, 13, 14, and 41 could be used to treat or prevent diseases, and how it could be used as a contraceptive or to detect sperm. Therefore, Applicants request that the written description rejection under 35 U.S.C. §112, first paragraph as to claims 5, 6, 13, 14, and 41 be reconsidered and withdrawn.

Response to rejections of claims 1-3, 7, 9-12, 15-19, 33-36, 39, 40, and 42 under 35 U.S.C. § 103(a), obviousness

Claims 1-3, 7, 9-12, 15-19, 33-36, 39, 40, and 42 stand rejected under 35 U.S.C. § 103(a) as obvious. It is the view of the Examiner that these claims are obvious over Herr et al. (U.S. Patent No. 5,830,472), in view of Owens et al. (J. Immunol. Methods, 1994, 168:149-165), and Bird et al. (Science, 1988, 242:423-426). Applicants respectfully traverse this rejection for the following reasons.

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

> the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

Additionally, MPEP § 2143.01 provides: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)."

None of these criteria have been met here. It would not have been obvious to combine the references. For example, none of the cited prior art suggests the desirability of the combination as required by *In re Mills*. Furthermore, none of the three references suggests or motivates one of ordinary skill in the art to combine or modify the references in an effort to arrive at the present invention. This opinion is shared by Dr. Thomas Moench, an expert in the field (Declaration provided herewith). The Examiner has presented no evidence that there was any motivation or suggestion in Herr et al., Owens et al., or Bird et al. to combine or modify these references, and therefore has not even established a *prima facie* case of obviousness.

The Examiner asserts that Herr et al. teaches the S19 monoclonal antibody produced by the hybridoma deposited as ATCC HB12144 and discloses methods for isolating and sequence regions of antibodies. The Examiner admits that Herr et al. does not specifically teach single chain Fv antibody fragments. Herr et al. does not teach the specific sequences of the present invention, nor does it disclose the single chain antibody of the invention. Herr et al. does not teach or suggest the use of a single chain antibody capable of binding to SAGA-1, consisting essentially of two specific sequences (i.e., SEQ ID NOs:1 and 3) which are bound to one another by a linker as recited in claim 1, nor does it suggest the other elements recited in the independent or dependent claims as asserted by the Examiner. As pointed out by the inventors in a prior response, the sequence of the light chain recited in Herr et al. was inaccurate. As discussed in the last response, a total of 31 nucleotides of the light chain sequence were incorrect as disclosed in Herr et al., relative to the correct sequence reported in the present application. Therefore, the defective sequence published in the Herr patent would not allow the

invention as claimed to be practiced. Furthermore, at column 9, lines 3-7, cited by the Examiner, Herr et al. merely states that the S19 monoclonal cDNA light and heavy chain sequences can be employed to provide recombinant antibodies. Herr et al. does not teach that recombinant sequences should be employed, while the present invention disclose the preparation and use of recombinant antibodies.

Additionally, contrary to the assertion of the Examiner, the statement in Herr et al. at column 3, lines 12-24 is merely speculation about making recombinant antibodies. Herr et al. in fact provides no recombinant antibodies. Thus, even if one of ordinary skill in the art would rely on a suggestion of Herr et al., they would not be able to practice the claimed invention because they would not be using the correct sequence. Moreover, Herr et al. does not provide such an antibody and was merely reciting a list of possible uses. Herr et al. does not suggest the specific antibodies as claimed in the present application, nor does Herr et al teach or suggest the other elements as claimed.

The statement by Herr et al., when analyzed in conjunction with the other references, would not have provided motivation to modify Herr or the other references, or to combine Herr with the other references cited by the Examiner. Furthermore, in the statement cited by the Examiner, Herr et al. was merely speculating about uses of antibodies or recombinant antibodies, while the present claims are composition claims, not method of use claims.

The Examiner asserts that Owens et al. teaches conventional techniques for genetic engineering of monoclonal antibodies for a variety of benefits, including to provide a more stable, higher-yield, and/or lower cost production means for the monoclonal antibodies than hybridomas. Owens et al., as a mini-review, merely encompasses the general state of the art of genetic engineering of monoclonal antibodies at the time it was published. Although Owens does suggest at page 155, second column, that Fvs may have an advantage over Fab fragments since they can be coupled to other effector molecular molecules, e.g., enzymes or drugs, without incurring a large penalty in terms of molecular size, this is merely speculation by Owens. Owens et al. does not teach or suggest the use of a single chain antibody capable of binding to SAGA-1, consisting essentially of two specific sequences (i.e., SEQ ID NOs:1 and 3) which are bound to one another by a linker as recited in claim 1, nor does it suggest the other

elements recited in the independent or dependent claims as asserted by the Examiner. Furthermore, contrary to the present invention, Owens et al. further teaches the deficiencies of a single chain recombinant antibody and suggests that a single chain recombinant antibody would not be useful because a single chain antibody has the characteristic of monovalent binding. Owens et al. further cites two studies to support the proposition that multivalent antibodies should be used and that single chain monovalent antibodies should not be used (see Owens et al., page 156). Therefore, based on the teachings of Owens et al, one of ordinary skill in the art would not be motivated to prepare and use a single chain antibody, and in fact would be motivated to use a multivalent antibody. In addition, because Owens teaches that a single chain monovalent antibody would not be effective, one of skill in the art would understand that even if a single chain antibody were prepared, there would not be a benefit such as decreased cost, as suggested by the Examiner. In fact, based on the teachings of Owens, one of skill in the art would believe that there would be no benefits in preparing such a single chain recombinant antibody. According to the teachings of Owens et al., the findings of the present application are unexpected.

The Examiner asserts that Bird et al. teaches production of single chain Fv fragments for a variety of benefits, particularly in clinical applications. The Examiner further asserts at page 4 of the Office Action that "the reference **confidently** predicted that active single-chain antigen-binding proteins could be produced from the sequence of any monoclonal antibody" (emphasis added). Bird et al. merely demonstrated that three specific monoclonal antibodies could be engineered to form single chains which still bind to their respective antigens. Bird et al. does not correct the deficiencies of Herr et al. and Owens et al. and does not teach or suggest the use of a single chain antibody capable of binding to SAGA-1, consisting essentially of two specific sequences (i.e., SEQ ID NOs:1 and 3) which are bound to one another by a linker as recited in claim 1, nor does it suggest the other independent or dependent claims asserted by the Examiner. Owens et al. published six years after Bird et al., but Owens merely cites Bird regarding linker use in constructing single chain molecules. Although Owens et al. cited Bird et al., it was not for the reasons cited by the Examiner. Even with knowledge of Bird et al., Owens et al. still teaches that single chain antibodies are not as useful because of reduced activity or

potency, relative to multivalent antibodies (see page 156 of Owens). Therefore, one of ordinary skill in the art at the time the application was filed would have appreciated that, even with the earlier teachings of Bird et al., Owens teaches away from the use of single chain antibodies and any potential benefits which were merely posited by Herr et al. and Bird et al. The suggestions in these references regarding potential benefits referred to by the Examiner were merely invitations regarding further experimentation and no data or teachings were provided to support the suggestions.

Because the there was not motivation or suggestion to combine or modify the cited references, and the references in fact teach away from the invention as claimed, there would be no reasonable expectation of success.

Further evidence that the claimed invention is not obvious over the references cited by the Examiner is the fact that the three references were published in 1998 (Herr et al.), 1994 (Owens et al.), and 1988 (Bird et al.), and that the present application was not filed until 2000. Thus, from the time Bird et al. published in 1988 until the present application was filed twelve years later, no one had conceived or reduced to practice the present invention as claimed. The invention as claimed was not obvious to one of ordinary skill in the art at the time the present application, because was filed there was no motivation or suggestion to combine Herr, Bird and Owens.

The Examiner has not identified anything in the references which would motivate or suggest to one of ordinary skill in the art to combine the teachings of the references. Furthermore, nothing in the references cited by the Examiner backs the assertion that it would be obvious to combine the references. An expert in the field, Dr. Thomas Moench, also agrees that it would not be obvious to combine the references (see Declaration submitted herewith). Therefore, it seems that the Examiner has used impermissible hindsight in formulating this rejection. There must be some logical reason apparent from the evidence of record that would justify a combination or modification of references. *In re Regel*, 188 USPQ 132 (CCPA 1975). In addition, Judge Linn stated in *In re Kotzab*, 217, F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000) regarding impermissible hindsight, that:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the

> prior art references and the then-accepted wisdom in the field. . . . Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."

Id. at 1369, citations omitted. Judge Linn goes on to state that:

> Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

Id at 1369, 55 USPQ2d 1316 (citations omitted).

Furthermore, even if the references were combined, the resulting combination is not the claimed invention. Thus, even if the references are combined, the resulting combination does not encompass all of the claim limitations. That is, the resulting combination is not a single chain antibody capable of binding to SAGA-1, consisting essentially of two specific sequences (i.e., SEQ ID NOs:1 and 3) which are bound to one another by a linker, nor does the combination encompass the elements of the dependent claims. Therefore, the cited art as a whole fails to teach or suggest the claimed invention within the meaning of 35 U.S.C. § 103(a).

Applicants submit that, for the foregoing reasons, claims 1-3, 7, 9-12, 15-19, 33-36, 39, 40, and 42 are not obvious under 35 U.S.C. § 103(a) as to Herr et al., Owens et al. and Bird et al. request that the rejection as to these claims be reconsidered and withdrawn.

Response to rejections of claim 38 under 35 U.S.C. § 103(a), obviousness

Claim 38 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious. It is the view of the Examiner that claim 38 is obvious over Herr et al. in view of Owens et al., and Bird et al., as discussed above, and further in view of Russell et al. (U.S. Patent No. 6,080,560). Applicants traverse the rejection for the following reasons.

None of the criteria set forth above regarding the three prong test for obviousness have been met here. The Examiner has not identified anything in the references which would motivate or suggest to one of ordinary skill in the art to combine the teachings of the references. Furthermore, nothing in the references cited by the Examiner backs the assertion that it would be obvious to combine the references.

Applicants respectfully submit that it would not have been obvious to combine the references. For example, none of the cited prior art suggests the desirability of the combination as required by *In re Mills*. Furthermore, none of the four references suggests to or motivates one of ordinary skill in the art to combine or modify the references in an effort to arrive at the present invention. This opinion is shared by Dr. Thomas Moench, an expert in the field (Declaration provided herewith). In section 8 of his Declaration, Dr. Moench states: "As a scientist, I can find nothing which connects the references in such a way as to make it obvious to combine them." The Examiner has presented no evidence that there was any motivation or suggestion in Herr et al., Owens et al., Bird et al. or Russell et al. to combine or modify these references, and therefore has not even established a *prima facie* case of obviousness. The general discussion set forth above regarding Herr et al., Owens et al., and Bird et al., applies with equal force here.

Contrary to the assertion of the Examiner, the mere fact that Russell et al. (U.S. Patent No. 6,080,560) teaches single chain antibodies produced in plants, the combination of Herr et al., Owens et al., and Bird et al., in view of Russell et al., does not render claim 38 obvious. Russell merely teaches that antibodies <u>can</u> be expressed in plant cells. Russell does not teach or suggest a host plant cell comprising heterologous DNA encoding a single chain Fv fragment selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:17 and SEQ ID NO:12, further wherein the host cell is a plant cell, as recited in claim 38 of the present application. As discussed above, Neither Herr et al., Owens et al., or Bird et al. teach or suggest a host cell comprising heterologous DNA encoding a single chain Fv fragment selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:17 and SEQ ID NO:12, further wherein the host cell is a plant cell, as recited in claim 38 of the present application. Therefore, Russell et al. does not correct the deficiencies of Herr et al., Owens et al., and Bird et al.

In addition, there is no motivation or suggestion in these references to use the teachings of Russell, nor is there a motivation or suggestion in Russell to adapt the teachings of Russell to the teachings of Herr, Owens, and Bird, as required by *In re Mills*. Nor do any of the references provide a motivation to combine the references. Further, as discussed above, Herr, Owens, and Bird do not provide any suggestion or motivation to combine those references. In fact, as described above in detail, Owens et al. teaches away from the present invention. Because the there was no motivation or suggestion to combine or modify the cited references, and the references in fact teach away from the invention as claimed, there would be no reasonable expectation of success.

Because Russell et al. does not correct the deficiencies of Herr et al., Owens et al., and Bird et al., the resulting combination of the four references is not the present invention. That is, even if combined, the references do not encompass the claimed elements of a host plant cell comprising heterologous DNA encoding a single chain Fv fragment selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:17 and SEQ ID NO:12, further wherein the host cell is a plant cell. Therefore, the combination of Herr, Owens, Bird and Russell cannot render claim 38 obvious.

Applicants submit that, based on the foregoing arguments, claim 38 is not obvious and request that the rejection as to this claim be reconsidered and withdrawn.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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